The organization of the central control of micturition in cats and humans
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The present thesis presents a new look at the basic circuitry of the micturition control system in cats and humans. Sensory information concerning bladder filling is relayed, via the pelvic nerve and dorsal root ganglion cells, to the sacral cord, where second order sensory neurons are located. These neurons convey the information to the caudal periaqueductal gray (PAG) where it is processed and filtered. When the amount of urine in the bladder makes voiding necessary, PAG neurons, provided that they are not inhibited by influences from other sources, activate the premotor interneurons in the M-region, which, via long descending fibers to the bladder motoneurons in the sacral cord, let micturition take place. The present chapter discusses the basic neural circuitry for micturition and continence in the context of the role of the forebrain, species differences and the emotional motor system. Finally, the role of the micturition circuitry in incontinence is discussed.

The basic micturition reflex in the cat

The results presented in this thesis suggest that the central control circuits for micturition and continence are organized separately and independently from each other (see also chapter 6). Both circuits are under strong control of the emotional motor system, while the voluntary or somatic motor system plays a much less prominent role (Fig. 1).

Micturition circuit

The bladder filling information from sensory neurons in the lumbosacral cord must finally reach the pontine micturition center (PMC) in order to empty the bladder at an appropriate time. In chapter 1 of this thesis it has been demonstrated that in the cat the lumbosacral cord does project only weakly to the PMC. On the other hand, the micturition reflex is not abolished by precollicular decerebration. Apparently, lumbosacral projections to forebrain areas, as thalamus and hypothalamus, are not essential for this reflex (Tang and Ruch, 1956). This observation, together with the finding that only very weak sacral cord projections exist to the PMC, leads to the conclusion that another brainstem region must serve as relay between sacral cord and PMC. The best candidate for such a relay center are the lateral and dorsal parts of the PAG. The lateral PAG is the only caudal brainstem structure known to project specifically to the PMC as shown in chapter 7, and stimulation of the PAG elicits complete micturition (Skultety, 1959). As demonstrated by Holstege et al. (1986) and in this thesis, activation of the PMC results in complete micturition. The projection from the PMC to the bladder parasympathetic motoneurons in the sacral cord is monosynaptic and excitatory (chapter 2), and is responsible for the bladder contraction during micturition. The monosynaptic and excitatory PMC projections to inhibitory GABA interneurons in the sacral dorsal gray commissure (DGC; chapter 3) are responsible for the inhibition of the motoneurons of the EUS during micturition. This is further substantiated by the observation that stimulation of the DGC results in a strong decrease in the intraurethral pressure (chapter 4).

Continence circuit

The urinary bladder in the cat fills towards a volume of about 40 ml (in humans several hundred ml) without a significant increase in intravesical pressure by passive adaptation of the bladder wall. The observed activation of the insular cortex (chapter 9), when the bladder is filled and the volunteers are not allowed to micturate, may indicate that the sympathetic system plays a role in the adaptation of the bladder to an increased urine volume. Activation of the right human
General Discussion

Fig. 1. Schematic overview of the ascending and descending pathways involved in the central control of micturition and continence. (+) = excitatory pathways; (-) = inhibitory pathways.
insula results in an increased sympathetic tone (Oppenheimer et al., 1992), and activation of sympathetic fibers has been shown to inhibit bladder wall mechanoreceptor discharge (Vaughan and Satchell, 1992). The result is a bladder wall relaxation leading to an increased bladder capacity. This is exactly what happened during the first condition of the PET studies prior to the micturition condition, when the volunteers had a filled bladder, but were not allowed to micturate. During the filling phase the striated EUS keeps the bladder closed. It is unknown what mechanism causes this tonic contraction of the EUS, but Blok and Holstege (1998) have put forward the concept that the L-region plays a crucial role. L-region neurons project bilaterally to the EUS motoneurons in the Onuf’s nucleus, and electrical stimulation in this area results in a contraction of the pelvic floor and an increased intraurethral pressure (Holstege et al., 1986). Bilateral lesioning of the L-region in the cat causes a chronic and extreme form of urge incontinence (Griffiths et al., 1990). In these animals only a few milliliters of urine in the bladder are sufficient to elicit a strong bladder contraction with a continuously relaxed EUS, suggesting an important role for the L-region in urinary continence. The importance of the L-region is also indicated by the PET activation of the L-region in human volunteers who were willing to micturate (chapter 8 and 9), but, because of emotional reasons, kept their sphincter tightly closed.

The next step in understanding the importance of the L-region in continence is to determine its afferents. Although at present nothing is known about them, it is most likely that they originate in limbic system related structures. Defining these structures is not an easy task, because the L-region is located in the area the ventral parabrachial and Kölliker-Fuse nuclei.

The voluntary motor cortical control of the pelvic floor as indicated in chapter 10 probably does not play a prominent role in normal urinary continence.

**Forebrain involvement in the control of micturition**

Although the forebrain is not essential for the basic micturition reflex, clinical observations suggest that it determines the beginning of micturition (Andrew and Nathan, 1964). In the cat, stimulation of forebrain structures as anterior cingulate gyrus, preoptic area of the hypothalamus, amygdala, bed nucleus of the stria terminalis and septal nuclei, elicits bladder contractions (Gjone, 1963). Many of these regions send fibers to the brainstem (Holstege, 1991), but only one region (the preoptic area) projects to the PMC (Holstege, 1987). The PET study on micturition in men and women (chapter 8 and 9) suggests that this is probably also true in humans, because during micturition the hypothalamus, including the preoptic area, showed an increased rCBF. This preoptic area, similar to the PAG, is known to play an important role in sexual behavior and contains a large number of estrogen and androgen receptor immunoreactive cells. Our own preliminary observations show that in the preoptic area of the uncastrated male cat a substantial number of the neurons containing androgen receptors project to the PMC. The importance of the preoptic area, which is better known for its role in sexual behavior, is further demonstrated by the observation that it receives a substantial projection from the sacral cord (unpublished observations of Blok and Holstege). The direct projection of the preoptic area to the PMC could be regarded as the final pathway for the emotional motor system to control the PMC and thus micturition. In this respect it must be kept in mind that micturition is an important tool in territorial demarcation and urine is a message in the framework of sexual behavior.
Species differences in the control of micturition

Micturition control is important in all mammals, but there exist a considerable variation in motor patterns. For example, when rats are taken out of their cage they immediately urinate. In contrast, cats, like humans, urinate very seldom in stressful situations. It is possible that these differences are reflected by a different neuronal control system. Recent light microscopical investigations by Ding et al. (1997) suggest that in the rat the sensory neurons in the lumbosacral cord project directly on neurons in the M-region. Preliminary ultrastructural results of Blok and Holstege on direct lumbosacral projections to the M-region of the rat confirm this observation. Apparently, micturition control is more “simply” organized in lower mammals as rodents, which is reflected in their different behavior.

Role of the cortex

The human PET scan results point to two cortical areas involved in micturition. The right dorsolateral prefrontal cortex is active when micturition takes place, but also when micturition is allowed but does not take place. The rCBF in the right anterior cingulate gyrus was significantly decreased during voluntary withholding of urine. Clinical work shows that forebrain lesions including the anterior cingulate gyrus are known to cause urge incontinence (Andrew and Nathan, 1964), and that certain urge incontinent patients had a hypoperfusion of the right frontal cortex (Griffiths, 1998). It remains to be elucidated how the prefrontal cortex and the anterior cingulate gyrus are precisely connected with the brainstem and hypothalamic micturition areas.

A striking observation in the PET studies on micturition (chapter 8 and 9) was that the cortical and pontine control areas are located predominantly on the right side, which corresponds with studies reporting that urge incontinence is correlated with lesions in the right hemisphere (Kuroiwa et al., 1987). Lesion experiments in the cat do not report a difference in importance between the left and right M-region (Griffiths et al., 1990; Mallory et al., 1991).

Future research directions

The results presented in this thesis provide insights in the central control of micturition, which open many new scientific and clinical possibilities. Research can be focused on the identified central structures in both the spinal cord and the brain. For example, the crucial role of the sacral inhibitory GABA-interneurons during micturition explains why intrathecially applied Baclofen (a GABA agonist) results in a relaxation of the bladder sphincter in paraplegic patients who suffer from dyssynergic micturition (Leyson et al., 1980). Possibly, intraspinally applied Baclofen aimed at motoneurons of the sphincter can help to reduce the side effects of the treatment.

Androgen and estrogen receptors in the preoptic area of the hypothalamus seem to be involved in the control of micturition. It has been suggested earlier that sex hormones play an important role in the control of micturition, but the clinical focus was, until now, exclusively aimed at the structures of the lower urinary tract, and not at the brain. Randomized trials with androgen and estrogen suppletion should be started in carefully urodynamically characterized urge incontinent patients in order to verify the involvement of sex hormones in the central control of micturition. PET scanning with estrogen and androgen ligands can establish the role of the hypothalamus in these hormonal treatments. Dynamic functional imaging is also important in treatment-effect evaluation in order to test whether these pharmacological treatments bring on functional changes in the brain structures, which dysfunction in urge incontinence.

Furthermore, it is likely that the beneficial effect on micturition observed in urge in-
continent patients after sacral nerve stimulation is the result of modulation of the brain structures (Tanagho and Schmidt, 1983). In order to verify this hypothesis PET scan experiments in incontinent patients are planned. The patients will have an implanted sacral nerve stimulator, which can be switched on and off during scanning. Eventually, these kind of experiments will lead to improved criteria for the selection of incontinent patients who might benefit from sacral nerve stimulation.

Epilogue
Urinary incontinence is an illness that considerably reduces the quality of life for those who suffer from it. An enormous number of elderly persons lose the ability to control urination (urge incontinence), which often places them in a socially isolated position. At least 10 million adults in the United States (Consensus conference, 1989) and about 4 million people in Germany suffer from urinary incontinence (Gesellschaft für Inkontinenzhilfe, 1997). It is estimated that up to 30% of elderly citizens in the United States suffer from urge incontinence. Of those living in a nursing home, the estimates are even higher, over 50%.

Only 40% are able to speak about their incontinence problem (Gesellschaft für Inkontinenzhilfe, 1997), because it is considered to be shameful. Therefore, incontinence is usually “hidden” by the people suffering from it. Apart from the social damage, urinary incontinence has also great economic implications. Already in 1982 it was estimated in the Washington Report that nursing homes in the United States spend more than $8 billion on incontinence. In 1987 the direct annual costs for care of patients with incontinence were estimated to exceed $10.3 billion in the United States only (Consensus Conference, 1989). These costs are primarily caused by symptomatic treatments like diapers and pharmaceutics, of which most are anticholinergic and aimed at the bladder itself. These treatments have many side effects and, in all likelihood, primarily serve as a placebo. They do not have an effect on the real cause of the incontinence, the dysfunctional brain. The most important goal of this thesis is to demonstrate the crucial role of the brain in the control of normal micturition, and that dysfunction of the identified brain areas probably causes incontinence in many elderly (see also Andrew and Nathan, 1964; Blaivas, 1982).